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(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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**Published**

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*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: ANTIFUNGAL COMBINATION THERAPY

(57) Abstract

There is described antifungal combination therapy comprising the use of known antifungal agents such as the azoles or polyenes in combination with a pneumocandin derivative antifungal agent. More particularly, the invention relates to antifungal combination therapy comprising the use of azoles such as fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346, SCH 56592;polyenes such as amphotericin B, nystatin or liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyoxins such as nikkomycins, in particular nikkomycin Z or other chitin inhibitors, elongation factor inhibitors such as sordarin and analogs thereof, mannan inhibitors such as predamycin, bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127 or complex carbohydrate antifungal agents such as CAN-296 in combination with a pneumocandin derivative as described herein.

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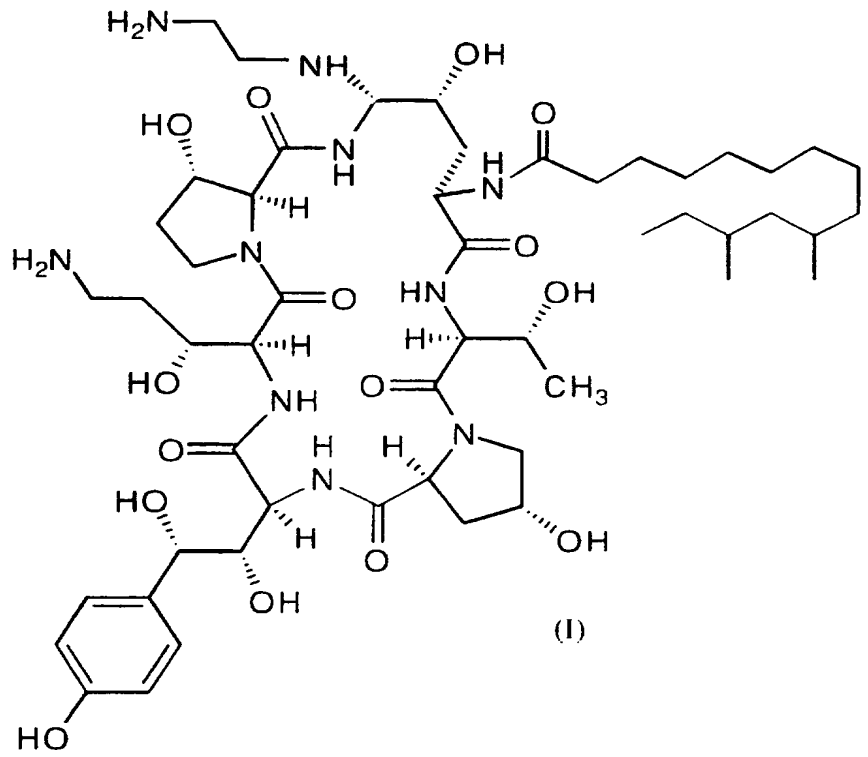
TITLE OF THE INVENTION

# ANTIFUNGAL COMBINATION THERAPY

FIELD OF THE INVENTION

The present invention relates to antifungal combination therapy comprising the use of known antifungal agents such as the azoles or polyenes in combination with a pneumocandin derivative antifungal agent. More particularly, the invention relates to antifungal combination therapy comprising the use of azoles such as fluconazole (hereinafter referred to as FCZ), voriconazole, itraconazole, ketoconazole, miconazole, ER 30346, SCH 56592; polyenes such as amphotericin B (hereinafter referred to as AmB), nystatin or liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyoxins such as nikkomycins, in particular nikkomycin Z or other chitin inhibitors, elongation factor inhibitors such as sordarin and analogs thereof, mannan inhibitors such as predamycin , bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127 or complex carbohydrate antifungal agents such as CAN-296 in combination with a pneumocandin derivative of the structure



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or a pharmaceutically acceptable salt or other pharmaceutically acceptable formulation thereof.

These combination therapies have been shown to be useful against such opportunistic pathogens as *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp., *Histoplasma* spp., *Coccidioides* spp., *Paracoccidioides* spp. *Blastomyces* spp., *Fusarium* spp., *Sporothrix* spp., *Trichosporon* spp., *Rhizopus* spp., *Pseudallescheria* spp., dermatophytes, *Paeciliomyces* spp., *Alternaria* spp., *Curvularia* spp., *Exophiala* spp., *Wangiella* spp., *Penicillium* spp., *Saccharomyces* spp., *Dematiaceous* fungi and *Pneumocystis carinii*.

## BACKGROUND OF THE INVENTION

There is an increasing need for agents which are effective against opportunistic mycotic infections by such agents as *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp., *Histoplasma* spp., *Coccidioides* spp., *Paracoccidioides* spp. *Blastomyces* spp., *Fusarium* spp., *Sporothrix* spp., *Trichosporon* spp., *Rhizopus* spp., *Pseudallescheria* spp.,

dermatophytes, *Paeciliomyces* spp., *Alternaria* spp., *Curvularia* spp., *Exophiala* spp., *Wangiella* spp., *Penicillium* spp., *Saccharomyces* spp., *Dematiaceous* fungi and *Pneumocystis carinii*. The present treatments, i.e., polyenes, such as amphotericin B, cause severe side effects and azoles, such as fluconazole, are only fungistatic. The pneumocandins, which are related to the echinocandins, are cyclic hexapeptides which inhibit cell wall 1,3ß-D-glucan synthesis. The pneumocandins have shown potent *in vivo* activity against *Candida* spp., *Pneumocystis carinii*, *Aspergillus* spp., as well as the other fungal pathogens listed above. However, the pneumocandins, by themselves, have weak activity against *Cryptococcus* spp.

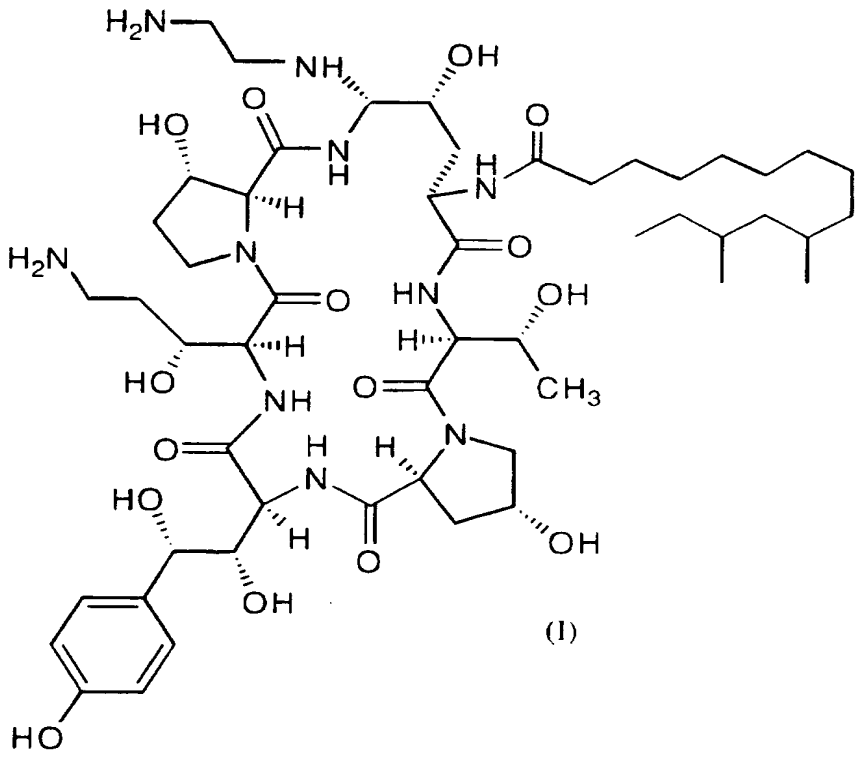
Combination therapy with antifungal drugs may provide additional options for treating *Cryptococcus* and other fungal pathogens.

Previous studies have evaluated the efficacy of other pneumocandin derivatives against *Cryptococcus neoformans* in combination with amphotericin B and fluconazole (Abruzzo et al., Antimicrob. Agents Chemo. 1995, 39:1077-1081 and Bartizal et al., Antimicrob. Agents Chemo. 1995, 39:1070-1076). However, none of these studies have demonstrated the results found using Compound I as the pneumocandin derivative.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to antifungal combination therapy comprising the use of known antifungal agents such as the azoles or polyenes in combination with a pneumocandin derivative antifungal agent. More particularly, the invention relates to antifungal combination therapy comprising the use of azoles such as fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346, SCH 56592; polyenes such as amphotericin B, nystatin or liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyoxins such as nikkomycins, in particular nikkomycin Z or other chitin inhibitors, elongation factor inhibitors such as sordarin and analogs thereof, mannan inhibitors such as predamycin , bactericidal/permeability-

inducing (BPI) protein products such as XMP.97 or XMP.127 or complex carbohydrate antifungal agents such as CAN-296 in combination with a compound of the structure



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or a pharmaceutically acceptable salt or other pharmaceutically acceptable formulation thereof.

In particular, this combination therapy has been shown to be useful against such opportunistic pathogens as *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp., *Histoplasma* spp., *Coccidioides* spp., *Paracoccidioides* spp. *Blastomyces* spp., *Fusarium* spp., *Sporothrix* spp., *Trichosporon* spp., *Rhizopus* spp., *Pseudallescheria* spp., dermatophytes, *Paeciliomyces* spp., *Alternaria* spp., *Curvularia* spp., *Exophiala* spp., *Wangiella* spp., *Penicillium* spp., *Saccharomyces* spp., *Dematiaceous* fungi and *Pneumocystis carinii*.

Compound I is disclosed in U.S. Patent No. 5,378,804. Its preparation is described in that patent along with U.S. Patent No. 5,552,521.

It is contemplated that other pneumocandin derivatives such as those disclosed in U.S. Patent No. 5,516,756 and in copending applications 07/936,558, 07/936,561, 08/058,657, 08/055,996, 08/378,687 and 60/006,505 would be useful in the combination therapy.

The azole, polyene or other antifungal agent may be administered orally or parenterally. Compound I is preferably administered parenterally, but is not limited to that route and may also be administered by other routes such as oral, intramuscular or subcutaneous.

As shown below, the combination therapy results in enhanced effects using sub-inhibitory concentrations of all agents. These effects can be demonstrated *in vitro* and *in vivo* using clinical and environmental strains of *C. neoformans*, *C. albicans* and *A. fumigatus*.

The invention is further described in connection with the following non-limiting examples.

## EXAMPLES

It has been found that combination therapy of Compound I with AmB and FCZ against *C. neoformans* results in enhanced activity against strains of *C. neoformans in vitro*. It has also been found that combination therapy of Compound I with AmB against *C. albicans* and *A. fumigatus* results in enhanced activity *in vitro*. This has been shown using a broth microdilution technique which is the standard method for antifungal susceptibility testing proposed by the NCCLS (protocol M27-T). Sub-inhibitory concentrations of Compound I in combination with sub-inhibitory concentrations of AmB and sub-inhibitory concentrations of FCZ were employed. The minimal inhibitory concentrations (MICs) for AmB and Compound I were defined as the lowest drug concentration at which there was an absence of growth. FCZ MIC was defined as the lowest drug concentration which resulted in a visual turbidity less than or equal to 80% inhibition compared with that produced by the control without antifungal agent.

Results of antifungal susceptibility testing show that colony forming units (CFUs) were markedly reduced when amphotericin B at certain concentrations (0.0075, 0.015 and 0.03 µg/ml) was combined with Compound I at certain concentrations (4, 8 and 16 µg/ml). Additionally, the administration of Compound I significantly enhanced the activity of fluconazole by reducing CFU numbers at certain concentrations (0.25, 0.50 and 1.0 µg/ml).

Additional drug combination testing *in vitro* was performed to evaluate combinations of Compound I with AmB and FCZ against clinical isolates. There was no antagonism evident between Compound I and AmB against *C. albicans*, *A. fumigatus* and *C. neoformans*. Fractional inhibitory indices (FIC) were approximately 0.50 or lower, indicative of additive or synergistic activity. Results suggest that Compound I can enhance the activity of FCZ and AmB and indicate a potential role for Compound I in combination regimes against those fungi less sensitive or insensitive to Compound I when used alone.

Drug interaction and efficacy studies with Compound I combined with either AmB or FCZ against disseminated candidiasis, aspergillosis and cryptococcosis were performed. Results showed no adverse effects with combinations at high, use or lower concentrations and no antagonism of efficacy with either AmB or FCZ combined with Compound I. Against *C. albicans*, Compound I doses of 0.03 mg/kg and lower plus 0.03 mg/kg and lower of AmB appeared more efficacious than either agent administered alone. With FCZ similar results were found at doses of 0.31 mg/kg and lower of FCZ when combined with 0.03 mg/kg of Compound I. Against *A. fumigatus*, significant improvements in efficacy (10 to >800-fold in ED values) with combinations were noted with Compound I titrated between 0.03 and 2 mg/kg and with AmB between 0.03 and 0.5 mg/kg. Significant improvement in survival was seen with Compound I at 0.008 mg/kg combined with AmB at 0.12 mg/kg over the compounds administered alone.

As found in drug combination studies *in vitro* with Compound I and AmB, FIC values were approximately 0.50, suggesting

additive or synergistic activity *in vivo*. Additionally, no antagonism of efficacy with FCZ in combination with Compound I was seen in studies against cryptococcosis in mice. Beneficial effects on efficacy were observed against *C. neoformans* with combinations of Compound I and FCZ at certain concentrations.

Given the above disclosure, it is thought that variations will occur to those skilled in the art. For example, it is thought that combination therapy using azoles other than fluconazole and pneumocandin derivatives other than Compound I may also be effective against fungal infections caused by the fungal pathogens noted. Accordingly, it is intended that the above examples should be construed as illustrative and that the invention disclosed herein should be limited only by the following claims.

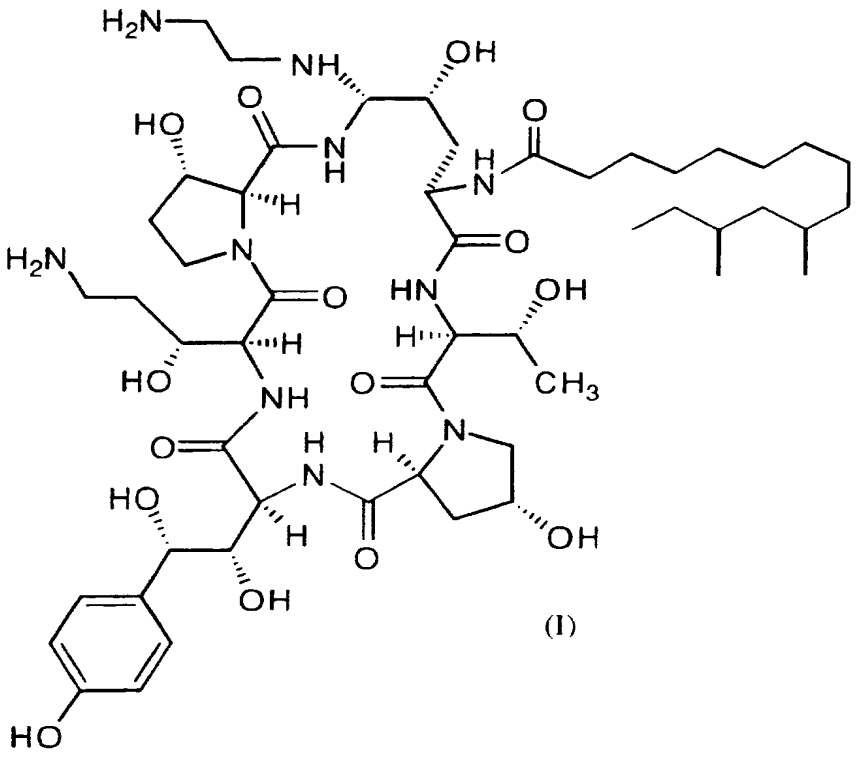
WHAT IS CLAIMED IS:

1. A method of treating fungal infection which comprises administering therapeutically effective amounts of a pneumocandin derivative and an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bactericidal/permeability inducing protein product or polyoxin.

2. The method of Claim 1 which comprises administering therapeutically effective amounts of a pneumocandin derivative and a polyene.

3. The method of Claim 1 which comprises administering therapeutically effective amounts of a pneumocandin derivative and an azole.

4. The method of Claim 1 wherein the pneumocandin derivative is



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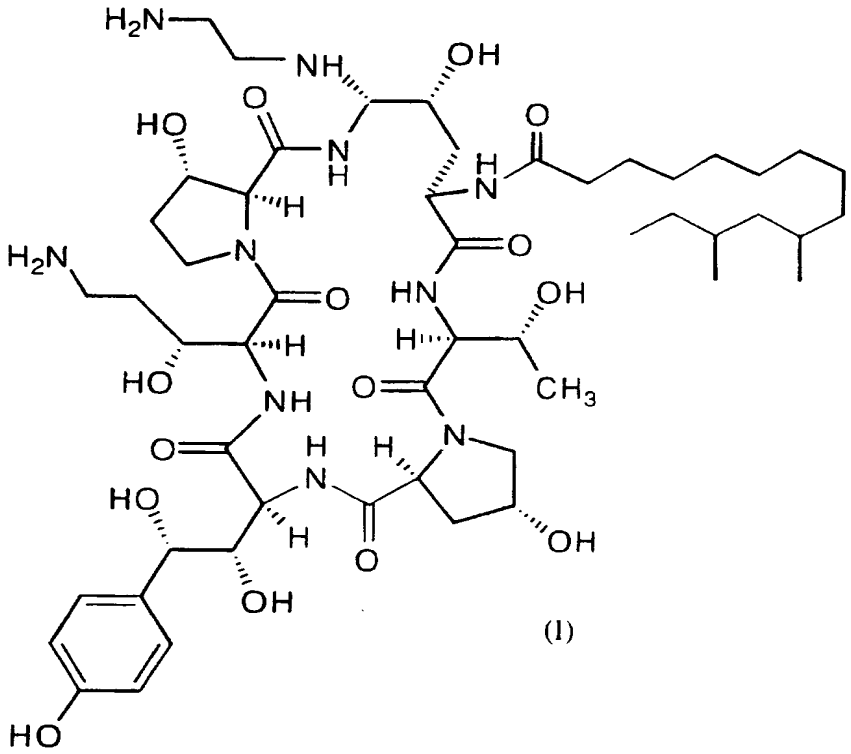
or a pharmaceutically acceptable salt thereof.

5. The method of Claim 2 wherein the pneumocandin derivative is



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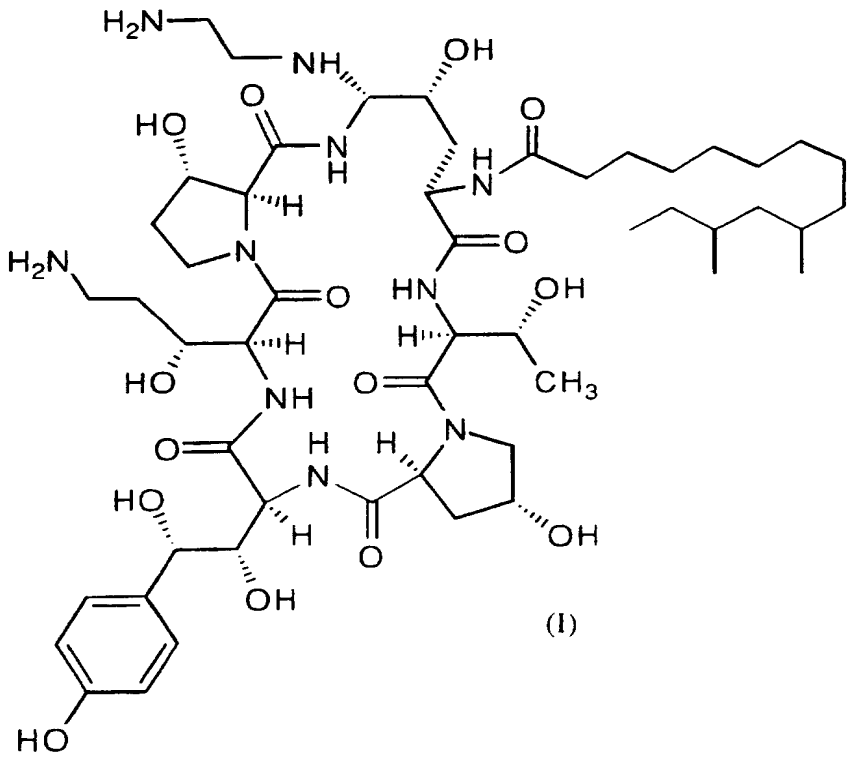
or a pharmaceutically acceptable salt thereof.

6. The method of Claim 3 wherein the pneumocandin derivative is



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or a pharmaceutically acceptable salt thereof.

7. The method of Claim 1 wherein the azole is selected from the group consisting of fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346, SCH 56592; the polyenes is selected from the group consisting of amphotericin B, nystatin or liposomal and lipid forms thereof; the purine or pyrimidine nucleotide inhibitors is flucytosine; the polyoxin is nikkomycin Z, the elongation factor inhibitor is sordarin and analogs thereof and the mannan inhibitor is predamycin.

8. The method of Claim 7 wherein the azole is fluconazole.

9. The method of Claim 7 wherein the polyene is amphotericin B.

10 The method of Claim 1 wherein the infection is caused by a fungal pathogen selected from *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp., *Histoplasma* spp., *Coccidioides* spp., *Paracoccidioides* spp. *Blastomyces* spp., *Fusarium* spp., *Sporothrix* spp., *Trichosporon* spp., *Rhizopus* spp., *Pseudallescheria* spp., dermatophytes, *Paeciliomyces* spp., *Alternaria* spp., *Curvularia* spp., *Exophiala* spp., *Wangiella* spp., *Penicillium* spp., *Saccharomyces* spp., *Dematiaceous* fungi or *Pneumocystis carinii*.

11. The method of Claim 2 wherein the infection is caused by the fungal pathogen selected from *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp., *Histoplasma* spp., *Coccidioides* spp., *Paracoccidioides* spp. *Blastomyces* spp., *Fusarium* spp., *Sporothrix* spp., *Trichosporon* spp., *Rhizopus* spp., *Pseudallescheria* spp., dermatophytes, *Paeciliomyces* spp., *Alternaria* spp., *Curvularia* spp., *Exophiala* spp., *Wangiella* spp., *Penicillium* spp., *Saccharomyces* spp., *Dematiaceous* fungi or *Pneumocystis carinii*.

12 The method of Claim 3 wherein the infection is caused by the fungal pathogen selected from *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp., *Histoplasma* spp., *Coccidioides* spp., *Paracoccidioides* spp. *Blastomyces* spp., *Fusarium* spp., *Sporothrix* spp., *Trichosporon* spp., *Rhizopus* spp., *Pseudallescheria* spp., dermatophytes, *Paeciliomyces* spp., *Alternaria* spp., *Curvularia* spp., *Exophiala* spp., *Wangiella* spp., *Penicillium* spp., *Saccharomyces* spp., *Dematiaceous* fungi or *Pneumocystis carinii*.

13. The method of Claim 10 wherein the fungal pathogen is selected from *Cryptococcus* spp., *Candida* spp. or *Aspergillus* spp.

14. The method of Claim 11 wherein the fungal pathogen is selected from *Cryptococcus* spp., *Candida* spp. or *Aspergillus* spp.

15. The method of Claim 12 wherein the fungal pathogen is selected from *Cryptococcus* spp., *Candida* spp. or *Aspergillus* spp.

# INTERNATIONAL SEARCH REPORT

Interna...nal Application No
PCT/US 97/15987

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/12 A61K45/06 //(A61K38/12,31:41),(A61K38/12,31:71)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | K. BARTIZAL ET AL.: "IN VITRO EVALUATION OF THE PNEUMOCANDIN ANTIFUNGAL AGENT L-733560, A NEW WATER-SOLUBLE HYBRID OF L-705589 AND L-731373." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 39, no. 5, May 1995, BETHESDA, MD, US, pages 1070-1076, XP002051763 cited in the application see page 1073, left-hand column, paragraph 2 | 1-3,7-15 |
| Y | see page 1075, left-hand column, paragraph 3 | 4-6 |
| | --- -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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# INTERNATIONAL SEARCH REPORT

Intern. ...nal Application No
PCT/US 97/15987

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 94 21677 A (MERCK & CO. INC.) 29 September 1994<br>see page 3, line 1 - page 4, line 15;<br>claims 1,3,12,14; examples 2,28-30<br>see page 4, line 25 - line 32<br>& US 5 378 804 A<br>cited in the application | 4-6 |
| P,X | S.P. FRANZOT ET AL.: "PNEUMOCANDIN L-743872 ENHANCES THE ACTIVITIES OF AMPHOTERICIN B AND FLUCONAZOLE AGAINST CRYPTOCOCCUS NEOFORMANS IN VITRO." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 41, no. 2, February 1997, BETHESDA, MD, US,<br>pages 331-336, XP002051764<br>see the whole document | 1-3,7-15 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No:
PCT/US 97/15987

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Remark : Although claims 1-15 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

# INTERNATIONAL SEARCH REPORT

information on patent family members

Intern. nal Application No
PCT/US 97/15987

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | ZA 9401807 A | 13-10-94 |